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Resectable Pancreatic Cancer With Peritoneal Metastases: Is Cytoreduction Combined With Hipec Effective and When?

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Abstract

Purpose: The purpose of the study is the presentation of the experience of one surgical team in patients with pancreatic cancer and peritoneal metastases treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) and a review of the literature.

Patients-Methods: The data of patients with pancreatic cancer and peritoneal metastases who underwent treatment with CRS plus HIPEC were analyzed. Clinical and histopathologic variables were correlated to survival, recurrence, and morbidity.

Results: In 10 patients (6 men and 4 women), with a mean age of 54.5+12.2 (28-72) years, 13 cytoreductions and HIPEC were undertaken for pancreatic cancer and peritoneal carcinomatosis. Complications were recorded in 8 patients, and 2 patients died in the perioperative period. The 1- and 3-year overall survival rates were 76% and 18%, respectively, and the median survival was 28 months. The completeness of cytoreduction and the performance status were related to survival ($p<0.05$). The recurrence rate was 69.2%. The gender and the presence of ascites were related to recurrence ($p<0.05$). Ascites has been identified as a possible prognostic indicator of recurrence ($p=0.027$).

Conclusion: There is evidence that CRS with HIPEC can increase survival in selected patients with pancreatic cancer and peritoneal metastases. Future studies are needed to identify the group of patients that will benefit from this treatment.

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Introduction

The peritoneum is the second most frequent site of pancreatic cancer after the liver. Peritoneal metastases are present in 14% of the cases at initial diagnosis [1]. At the time of death, peritoneal carcinomatosis is identified in 50% of the cases [2][3]. Improvements in systemic chemotherapy have increased the overall survival of patients with peritoneally disseminated pancreatic cancer, but it still remains low and does not exceed 9 months [4]. Peritoneal dissemination is classified as stage IV disease, and only systemic palliative chemotherapy has been used until recently [5].

CRS with HIPEC has been an effective treatment strategy for many diseases with peritoneal dissemination[6][7][8][9][10]. CRS is performed with the intent of resecting the entire macroscopically visible tumor, and HIPEC is integrated in CRS with the intent to eradicate the microscopic residual tumor, which always remains at the peritoneal surfaces even after complete cytoreduction. The use of HIPEC has been shown to be feasible and safe after pancreatic resection [11][12].

The extent of peritoneal disease and the completeness of cytoreduction have been identified as the most significant variables of survival in diseases presenting with peritoneal malignancy [7][8][9][10]. The most recent publication with pancreatic cancer and peritoneal metastases has shown excellent results in properly selected patients with a limited extent of peritoneal disease who underwent complete cytoreduction without a macroscopically visible residual tumor [13]. The presence of metastatic liver disease in pancreatic cancer is no longer considered unresectable disease [14]. A sub-group of patients with liver metastatic disease of pancreatic cancer origin may be offered a significant survival benefit from surgery. The limit of surgery in these situations is still unknown.

The purpose of the present study is to update the results of a surgical team with a limited experience in the treatment of pancreatic cancer with peritoneal metastases and to review the literature.

Patients-Methods

The data of the patients with peritoneal malignancy from pancreatic cancer was retrospectively reviewed in a prospectively maintained database. The patients were treated in an accredited Department of Surgical Oncology specialized in Peritoneal Surface Malignancy by the same surgical and anesthesiological team. All patients signed an informed consent

indicating that the treatment was individualized, was not in routine practice, and did not provide established benefit. The Ethical Committee of the Hospital approved the protocol.

Preoperative work-up included a physical examination, hematologic-biochemical examinations, tumor markers (CEA, CA 19-9, CA-125), abdominal and thoracic CT scanning with the intent to assess the presence of unresectable metastatic disease, identify precisely the site of implants, and calculate the extent of the peritoneal disease. The performance status was assessed according to the Karnofsky performance scale. The anesthesiological assessment classified the patients according to ASA stage. Diagnostic laparoscopy and/or CT-enteroclysis were also used in those cases in which the extent of the peritoneal disease at the small bowel was inconclusive. The presence and the volume of ascites were recorded in detail. The location of the primary tumor was also recorded. The extent of prior surgery was recorded using the prior surgery score (PSS). PSS-0 defined the patients who had not undergone surgery previously. PSS-1 defined those patients who had undergone biopsy or surgery in one abdominopelvic region, PSS-2 defined surgery in 2-5 abdominopelvic regions, and PSS-3 defined surgery in > 5 regions [15]. The tumor volume was also assessed. LS-0 defined no visible implant on a specific abdominopelvic region. LS-1 defined the presence of implants with their largest diameter < 0.5cm. LS-2 defined the presence of implants with the largest diameter > 0.5 cm and < 5 cm, while LS-3 defined implants with their largest diameter > 5 cm or confluent implants of any size. Patients with implants LS-1 were considered as having small volume tumors, and those with implants LS-2 and LS-3 as having large volume tumors.

Eligibility criteria

Patients over 16 years, with acceptable performance status (Karnofsky scale > 50%), ASA-stage < III, with normal renal function (blood urea < 50 mg/dl, and creatinine < 1.5 mg/dl), WBC > 4000, platelets > 100,000, normal hepatic function, and capable of undergoing major surgery were considered eligible for treatment. Patients with a recent history of cardio-pulmonary disease, poor performance status (Karnofsky scale < 50%), ASA-stage >III, or with an abnormal renal-hepatic-hematologic profile were excluded from treatment. Extensive seeding of the mesentery of the small bowel or infiltration of the antimesenteric edge of the small bowel were also exclusion criteria.

Surgery

A midline incision extending from the xiphoid process to the symphysis pubis was used for maximal exposure of the abdominal cavity. The extent of the peritoneal disease was calculated using the peritoneal cancer index (PCI) after the lysis of the adhesions. Cytoreductive surgery was possible using the standard peritonectomy procedures [16]. The completeness of cytoreduction was calculated after tumor resection according to Sugarbaker's criteria [15]. Radio-frequency ablation (RFA) was used for the eradication of liver metastatic lesions. HIPEC was administered with the Coliseum technique (open abdominal technique) with a continuous closed circuit of four drains (two inlet and two outlet), one heat exchanger, and two roller pumps connected to the inlet and outlet drains (Sun-Chip, Gamida Tech, Paris, France). The cytostatic drugs were administered diluted in 2-3 liters of Normal Saline or Ringer's Lactate at 42.5-43^{0}C. HIPEC with gemcitabine was performed for 60 min and with Mit-C for 90 min. The reconstruction of the continuity of the

alimentary tract was always performed after the completion of HIPEC.

All patients remained in the ICU for at least 24 hours after surgery. Postoperative complications were carefully recorded and classified according to the Clavien-Dindo classification [17].

All specimens were histopathologically examined in detail. The histologic subtype was defined. The number of resected and infiltrated lymph nodes was also recorded, as well as the infiltration of nerves and veins.

Follow-up

The patients were followed every 4 months for the first year and every 6 months later until death with physical examination, hematological-biochemical examinations, tumor markers (CEA, CA 19-9, CA-125), and radiologic examinations (thoracic and abdominal CT-scan). The time and the site of recurrence were recorded.

Statistics

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences, version 17.0). The proportions of patients with a given characteristic were compared by x^2 or by Pearson's test. Differences in the means of continuous measurements were tested by the Student's t-test. The Kaplan-Meier method was used for the construction of survival curves. The comparison of curves was possible using the log-rank test. Multivariate analysis of survival was assessed with the Cox proportional hazard model for the identification of the prognostic variables of survival. Logistic regression analysis was used to identify the prognostic variables of recurrence and morbidity. A two-tailed p value < 0.05 was considered statistically significant.

Results

The files of 10 patients (6 men and 4 women) with pancreatic cancer and peritoneal metastases who underwent 13 cytoreductions from 2011-2018 were retrieved. The mean age of the patients was 54.5+12.2 (28-72) years. Three patients underwent secondary cytoreduction additionally because of recurrence.

The general characteristics of the patients are listed in Table 1. The primary tumor was located in the pancreatic tail in all cases. The mean PCI was 10±5 (3-20). All patients had a large volume tumor, and 5 of them had ascites. Three patients were identified with peritoneal metastases at the initial diagnosis, and one of them had 6 synchronous hepatic metastatic lesions, while the others were found with metachronous peritoneal metastases. Two patients with a large volume tumor in the small bowel were not considered candidates for CRS at the time of initial diagnosis and received neo-adjuvant chemotherapy. Both patients responded after 4 cycles of chemotherapy and underwent CRS plus HIPEC. In addition, two women had been previously treated with CRS and systemic chemotherapy for ovarian cancer. The radiologic examinations were inconclusive about the origin of peritoneal carcinomatosis. The tail of the pancreas was enlarged without any obvious tumor in both patients. Complete cytoreduction (CC-0) was possible in 11 cases. An epigastric

peritonectomy procedure (resection of the previous scar with the round and the falciform ligaments of the liver) was undertaken in 1 case. Right and left subdiaphragmatic peritonectomies were undertaken in 5 and 3 cases, respectively, greater and lesser omentectomy in 7 and 5 cases, respectively, and splenectomy in 5 cases. Cholecystectomy was undertaken in 4 cases, and resection of the omental bursa in 4 cases. Right and left lateral peritonectomy procedures were required in 5 and 4 cases, respectively, while a pelvic peritonectomy was necessary in 6 cases. In addition, subtotal gastrectomy was undertaken in 3 cases, subtotal colectomy in 2, segmental intestinal resection in 3, right colectomy in 1, hepatic RFA in one case, and in another one, resection of the left kidney was required in order to achieve CC-0 surgery. A distal pancreatectomy was undertaken in 5 cases. In 2 cases, a distal pancreatectomy had been previously performed and an additional pancreatectomy was needed for a CC-0 surgery. One patient was treated with palliative surgery (CC-3). The patient presented with a complete obstruction of the small bowel and underwent a by-pass procedure because of the extensive peritoneal seeding of the small bowel, although a CC-0 surgery had been previously performed. This patient did not receive HIPEC. In 7 cases, gemcitabine (1000mg/m^2) was used during perfusion, and in 3 cases, a combination of cisplatin (50mg/m^2)+Mit-C (10mg/m^2) was used. Postoperative systemic chemotherapy with gemcitabine was administered in 8 cases. The diagnosis of pancreatic ductal adenocarcinoma was established in 11 specimens by histopathology. Peri-pancreatic lymph nodes were positive in all specimens. A pancreatic adeno-squamous tumor was diagnosed by histopathology in one patient who underwent CRS and HIPEC twice because of recurrence.

Complications were recorded in 8 cases (61.5%) (Table 1). Two patients had Grade 1 complications, one patient had a Grade 2 complication, 3 had Grade 3, and 2 had Grade 5 complications. One patient, who was a heavy smoker, required prolonged mechanical ventilation due to pulmonary insufficiency. The same patient developed recurrence in one year, and despite treatment with systemic chemotherapy, he underwent secondary CRS and HIPEC. He died at the 5th postoperative day because of acute hepatic failure. One patient who underwent CRS and HIPEC twice presented severe bile esophagitis as a result of upper gastrectomy and esophagogastric anastomosis. Another patient was complicated by an enterocutaneous fistula, and two more patients presented intra-abdominal abscesses because of pancreatic leaks (one of them presented with a delayed abscess 4 months after surgery). One more patient died on the 6th postoperative day due to renal failure as a result of intraoperative hemodynamic instability.

Survival

The median survival was 28 months. The 1- and 3-year overall survival rates were 76% and 18%, respectively (Figure 1). Univariate analysis of survival showed that the completeness of cytoreduction and the performance status were correlated to survival (Table 2). Multivariate analysis did not identify any possible prognostic variable of survival. No variable was found to be related to morbidity (Table 2). The median disease-free survival was 23 months.

Follow-up

The median follow-up time was 11 months (3-38). Recurrence was recorded in 9 cases (69.2%). There were 5 distant (38.5%) and 4 local-regional recurrences (30.8%). The gender (p=0.039) and the presence of ascites (p=0.039) were

found to be related to recurrence by univariate analysis. The presence of ascites (p=0.027) has been identified as a possible prognostic variable of recurrence by multivariable analysis.

Currently, 1 patient (9.1%) remains alive without disease 38 months after initial treatment, 5 (45.5%) died because of disease recurrence, 1 patient (9.1%) died because of reasons unrelated to the disease, and 4 patients (36.4%) are alive with disease recurrence.

Discussion

Despite improvements in the outcomes of pancreatic cancer surgery, the overall survival has not significantly increased. The results of the administration of chemotherapy (adjuvant or neo-adjuvant), or immunochemoradiotherapy are controversial [18]. Up to 70% of patients with surgical resection develop local-regional recurrence in 2-3 years[19]. The 5-year survival after R_0 resection combined with multimodality treatment does not exceed 20% in high-volume and specialized centers [20].

Until recently, patients with metastatic pancreatic cancer were excluded from surgery[18]. The synchronous resection of both the primary and the peritoneal metastatic tumors appears to offer a significant survival benefit [13][14]. The untreated peritoneal metastases of pancreatic cancer origin usually lead very soon to intestinal obstruction, ascites, and malnutrition [21].

The pathophysiology of peritoneal metastases remains unclear. Cancer emboli exfoliated from the surface of the primary tumor, which has disrupted the pancreatic serosa, move to remote sites assisted by peritoneal fluid movement, intestinal motility, and gravity. Some of them are implanted at the peritoneal surfaces, and others are absorbed by the greater and lesser omentum or the hemidiaphragms and progress to visible peritoneal metastases. Low-volume local disease progresses to visible peritoneal implants in patients who have been left with positive margins of resection. In addition, cancer emboli originate from the traumatized interstitial tissues located within narrow limits of resection, or from the transected lymphatic network, or even from venous blood lost during surgical manipulations. During wound healing, the emboli entrapped in fibrin attract inflammatory cells and collagen and are stimulated by growth factors that give rise to recurrent tumors in 2-3 years [22]. Systemic chemotherapy is ineffective in the control of local-regional recurrence[23] in contrast to experimental work which has shown that the intraperitoneal administration of gemcitabine may effectively control the local-regional microscopic tumor [24]. A high drug level with low systemic exposure is achieved by the intraperitoneal administration of cytostatic drugs [25], while the high concentration of the absorbed drug in the portal circulation may be effective in eradicating micrometastatic hepatic disease [26]. There is evidence from previous clinical studies that the local-regional control of the microscopic residual pancreatic tumor is possible with intraperitoneal chemotherapy [27][28][29].

Farma et al. presented discouraging results in an older study in which a small number of patients with gastric, duodenal, and pancreatic cancer were included together [30]. The beneficial effect of CRS and HIPEC has been shown in a previous report of case series. In this study, there was no limit in regard to the extent of the peritoneal disease, and long-term

survival was reported even for patients with extensive disease who did not undergo complete cytoreduction. All tumors were located at the tail of the pancreas [31]. In a recent comparative study, Gudmundsdottir et al. showed that patients with limited peritoneal extent undergoing complete cytoreduction and HIPEC have 1-, 2-, and 3-year survival rates of 91%, 66%, and 59%, respectively, with the longest survivor at 54 months without evidence of disease. The results are outstanding, showing that pancreatic cancer with peritoneal metastases is not always a lethal disease, and possibly there is hope for long-term survival for a subgroup of patients. In this study, the group of CRS plus HIPEC consisted of 5 patients with tumors of the head of the pancreas and 18 with tumors of the tail [13]. These results are in contrast to Artinyan et al., who have shown that patients with tumors of the body and tail of the pancreas have a worse prognosis than those with tumors of the head and are associated more frequently with hepatic metastases [32]. Gudmundsdottir et al. strongly support the routine use of preoperative laparotomy in every patient with pancreatic cancer with the intent to identify small volume peritoneal metastases which are otherwise undetectable by imaging techniques. These patients, as well as those with positive peritoneal cytology without visible peritoneal metastases, may undergo complete CRS and HIPEC. Another option for detecting small peritoneal metastases undetectable with conventional imaging is the use of CT enteroclysis, which has 92% sensitivity, 96% specificity, 97% positive predictive value, and 91% negative predictive value in the assessment of peritoneal metastases at the small bowel and its mesentery [33]. There is much evidence that CRS and HIPEC are effective in the treatment of pancreatic cancer with peritoneal metastases. However, the cut-off point of the PCI has not yet been identified. The completeness of cytoreduction score is the most significant prognostic variable for long-term survival, regardless of the primary tumor origin [6][7][8][9][10]. Our limited experience has shown that there are patients undergoing incomplete (CC-1) cytoreduction who may be offered a significant survival benefit from CRS and HIPEC [31]. In our updated study, we included one patient with large volume peritoneal disease and hepatic metastatic lesions who underwent complete cytoreduction and complete ablation of the hepatic disease and survived 28 months. There is much evidence that pancreatic cancer resection may be performed concurrently with liver metastatic disease [14]. Simultaneous resection of liver metastatic disease and colorectal cancer has been shown to be feasible and beneficial [34]. Future studies are needed to answer if patients with resectable pancreatic cancer and synchronous peritoneal and liver metastases may be offered a survival benefit by undergoing simultaneous resection or ablation to CRS and HIPEC.

The rate of morbidity was high. Univariate analysis did not reveal any variables related to morbidity. The ASA stage is probably an exception because it showed a trend to correlate to morbidity (p=0.057). In a recent review study, Brind'Amour et al. have reported that CRS and HIPEC appear to be a safe method, conferring the same rate of morbidity and mortality as surgery for pancreatic cancer without peritoneal metastases. The method appears to offer local control in highly selected patients [35]. No hematologic toxicity was recorded, in contrast to Satoi et al., who reported 42% hematologic toxicity Grade ¾ and 18% non-hematologic adverse effects [36]. Despite the use of systemic chemotherapy, the rate of recurrence was high (69.2%) with a small prevalence of distant metastases.

Conclusions: This is a case series study that does not intend to draw definitive conclusions about the use of CRS and HIPEC in pancreatic cancer patients with peritoneal metastases. The international literature and the present study provide evidence suggesting that CRS and HIPEC may be safely used in the treatment of these patients. It remains unclear what

the subgroup of patients is that may be offered a significant survival benefit. Hopefully, this is the challenge for the future.

Figures and Tables

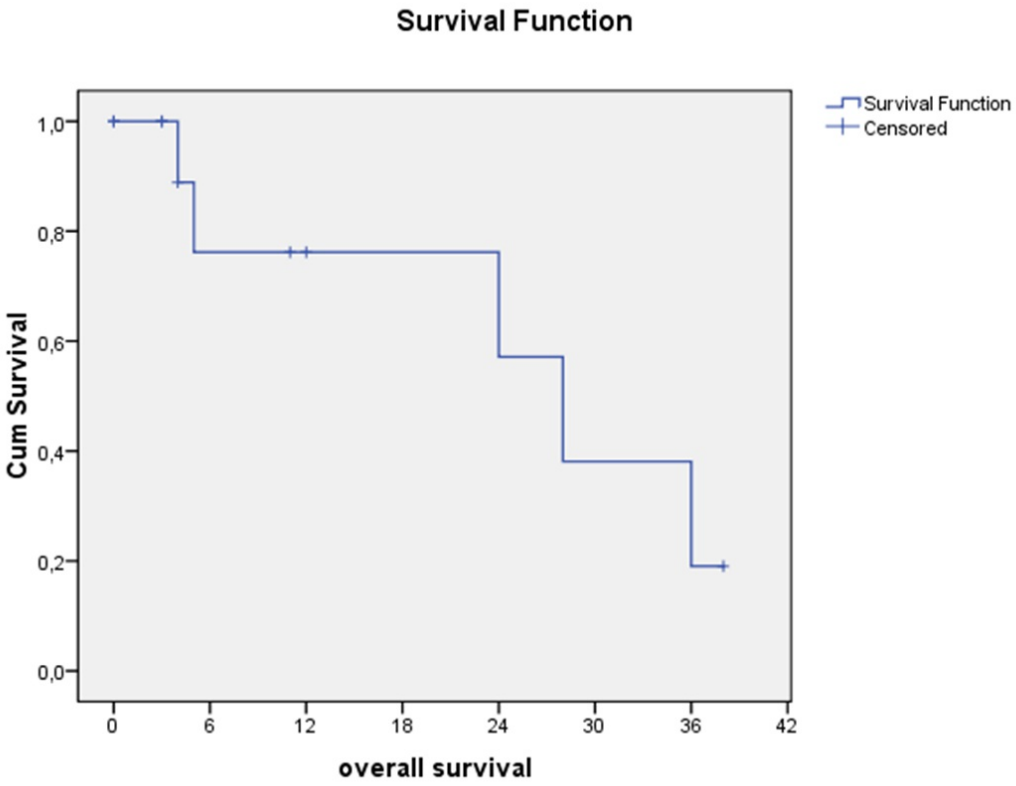

Figure 1. Overall Survival

Table 1. General characteristics

	No of pts	%
Tumor volume		
Large volume	13	100
Small volume	0	0
ascites	5	38.5
PSS		
PSS-0	5	38.5
PSS-1	0	0
PSS-2	5	38.5
PSS-3	3	3
PCI		
<13	9	69.2
>13	4	30.8
CC		
CC-0	11	84.6
CC-1	1	7.7
CC-2	0	0
CC-3	1	7.7
morbidity	8	61.5
mortality	2	15.4
recurrence	9	69.2
Site of recurrence		
Distant	5	38.5
Local-regional	4	30.8

Table 2. univariate analysis of survival

	survival	morbidity
variable	P value	P value
Gender	0.93	0.569
PSS	0.143	0.42
PCI	0.475	0.569
CC	0.012	0.151
Performance status	0.018	0.42
ASA stage	0.561	0.057
age	0.838	0.224
ascites	0.523	0.279
morbidity	0.109	

Table 3. analysis of recurrence

Univariate analysis		**Multivariate analysis**
variable	P value	P value
Gender	0.039	
PSS	0.231	
PCI	0.338	
CC	0.762	
Morbidity	0.164	
Performance status	0.415	
ASA stage	0.425	
age	0.197	
ascites	0.039	0.027

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